UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/420,433 | 10/12/1999 | DAVID SIDRANSKY | JHU1180-1 | 2810 |

7590 01/06/2006

Lisa A. Haile
Gray Cary Ware & Freidenrich LLP
4365 Executive Drive
SUITE 1100
San Diego, CA 92121-2133

| EXAMINER | |
|---|---|
| JOHANNSEN, DIANA B | |
| **ART UNIT** | **PAPER NUMBER** |
| 1634 | |

DATE MAILED: 01/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/420,433 | SIDRANSKY, DAVID | |
| | Examiner | Art Unit | |
| | Diana B. Johannsen | 1634 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *01 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-4,7-14,18-22,24-26 and 28-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7-14,18-22,24-26 and 28-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

1. A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on September 1, 2005 has been entered.

Claims 1, 20, and 25 have been amended and claims 28-31 have been added. Claims 1-4, 7-14, 18-22, 24-26, and 28-31 are now pending and under consideration.

### *Claim Rejections - 35 USC § 112, second paragraph*

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-4, 7-11, 20-22, 24-26, and 28-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-4, 7-11, 20-22, 24-26, and 28-31 are indefinite over the recitation of the phrase "does not exhibit microscopic characteristics indicative of neoplastic pathology" in claims 1, 20, 25, and 28-31. It is noted that the specification does not define, or even employ, the term "microscopic characteristics," and that the prior art does not provide a standard meaning or definition for this term as it relates to the identification of neoplastic

cells using a microscope. While the specification exemplifies the detection of (and failure to detect) cancer by light microscopy (see Examples beginning at page 35 of the specification), many types of microscopy may be employed in identifying cancer cells, and additional techniques such as staining, labeling, etc., may be employed with microscopy to increase its sensitivity. It is not clear whether the recitation "does not exhibit microscopic characteristics indicative of neoplastic pathology" encompasses characteristics determined by any type of microscopic method, whether this language refers to characteristics apparent by light microscopy only, by light microscopy with additional techniques (labeling, staining, etc.), etc. Accordingly, the manner in which this language limits the claims cannot be ascertained, rendering the claims vague and indefinite.

***Claim Rejections - 35 USC § 112 – new matter***

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-4, 7-11, 20-22, 24-26, and 28-31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 1, 20, and 25 have been amended so as to recite the phrase "does not exhibit microscopic characteristics indicative of neoplastic pathology," and new claims 28-31 also employ this language. The originally filed specification does not provide basis for this new limitation. The specification does exemplify the detection of (and failure to detect) cancer by light microscopy, and the originally filed claims did make reference to, e.g., a specimen that "does not exhibit morphological characteristics indicative of neoplastic pathology" (see, e.g., original claim 1) and tissue that "appears normal under a microscope" (see, e.g., claim 14). However, the term "microscopic characteristics" was not employed in the specification as originally filed, and is not, e.g., a synonym of "morphological characteristics" or simply a rewording of a term or concept disclosed in the specification. The meaning of this language is not clear (as discussed in the immediately preceding rejection), and the specification does not discuss or describe what would constitute a specimen that "does not exhibit microscopic characteristics indicative of neoplastic pathology." It is further noted that Applicant's response does not identify where in the specification basis for this language is believed to be located. Accordingly, the addition of this language to the claims constitutes the addition of new matter.

***Claim Rejections - 35 USC § 112, enablement***

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-4, 7-14, 18-22, and 24-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is first noted that those claims which previously included the limitation "does not exhibit morphological characteristics indicative of neoplastic pathology" have now been amended so as to instead include the limitation "does not exhibit microscopic characteristics indicative of neoplastic pathology" (see in particular claims 1, 20, and 25 as amended 01 September 2005). It is further noted that this rejection applies to **claims 12-13 and 18-19** to the extent that those claims may be limited to a specimen that "does not exhibit microscopic characteristics indicative of neoplastic pathology" (see, e.g., claim 1) and/or to tissues that "appear normal under a microscope" (as in dependent claim 14)

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (A) the breadth of the claims; (B) the nature of the invention; (C) the state of the prior art; (D) the level of one of ordinary skill; (E) the level of predictability in the art; (F) the amount of direction provided by the inventor; (G) the existence of working examples; and (H) the quantity of experimentation needed to make

or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (*MPEP* 2164.01(a)).

Claims 1-4 and 7-11 are drawn to methods in which a "mutant target nucleic acid" selected from APC, DCC, NF1, NF2, RET, VHL, and WT-1 is detected in a tumor margin tissue specimen that is "external to a primary neoplasm" and which "does not exhibit microscopic characteristics indicative of neoplastic pathology." Claims 12-14 are drawn to methods in which a "neoplastic nucleic acid having a mutant nucleotide sequence" that is selected from APC, DCC, NF1, NF2, RET, VHL, and WT-1 is detected in a surgical margin by oligonucleotide hybridization. Claim 18 encompasses detection of such a neoplastic nucleic acid in a "tissue specimen which is external to a primary neoplasm," while claim 19 requires the presence of such a sequence in a "tumor margin tissue specimen." Claims 20-22 and 24 are drawn to methods in which a "mutant target nucleic acid" selected from APC, DCC, NF1, NF2, RET, VHL, and WT-1 is detected in a "lymph node tissue specimen" that is "external to a primary neoplasm" and which "does not exhibit microscopic characteristics indicative of neoplastic pathology." Claims 25-26 are drawn to methods in which a "neoplastic nucleic acid having a mutant nucleotide sequence" that is selected from APC, DCC, NF1, NF2, RET, VHL, and WT-1 is detected in lymph node tissue by oligonucleotide hybridization, wherein the lymph node is "external to a primary neoplasm" and "does not exhibit microscopic characteristics indicative of neoplastic pathology."

It is unpredictable as to whether one of skill in the relevant art could use the invention of the instant claims. The claims as written require that each of the

"neoplastic" or "mutant" nucleic acids recited therein may be detected in tumor margins and lymph node tissues that do not "exhibit microscopic characteristics indicative of neoplastic pathology." However, the specification only exemplifies the detection of a different mutated nucleic acid, p53, in surgical margins and lymph nodes that appear histologically normal by light microscopy in patients afflicted with head and neck squamous cell carcinoma (see Examples 1-4, as well as Figures 2-5 and 7-9). It is again noted that (as discussed above) the term "microscopic characteristics" was not employed in the specification as originally filed, and is not, e.g., a synonym of "morphological characteristics" or simply a rewording of a term or concept disclosed in the specification. Applicant's specification does not provide any evidence that mutated versions of any of the nucleic acids recited in the instant claims were -- or can be -- detected in any type of sample (from any type of patient, with any type of cancer) that "does not exhibit microscopic characteristics" of any kind that are indicative of neoplastic pathology. Many types of microscopy were available for use by those of skill in the art at the time the invention was made, and additional techniques such as staining and labeling may be employed with microscopy to increase its sensitivity. Given the absence of evidence and data provided in the specification regarding the detection of the nucleic acids of the claims in any type of sample with any type of "microscopic characteristics," it is completely unpredictable as to whether said nucleic acids may in fact be detected by the methods of the claims in samples having no "microscopic characteristics indicative of neoplastic pathology." With further regard to claims 12-14, it is further noted that the specification is also silent with regard to detection of any of

these nucleic acids in any type of tissue that "appears normal under" any type of microscope. Lacking guidance from the specification, one of skill in the art may looking to the teachings of the art for further guidance and enablement of a claimed invention. However, in the instant case, the prior art is also silent with respect to any teachings that mutant versions of any of the genes of the instant claims may be detected in, e.g., surgical margins or lymph nodes that have no "microscopic characteristics indicative of neoplastic pathology." The closest prior art reference, Nees et al (Cancer Research 53(18):4189-4196 [9/1993]), discloses that mutated p53 nucleic acids were detected in tumor margin specimens obtained from patients with head and neck cancers (see, e.g., Table 3, p. 4191, 4193). However, Nees et al note that their findings with p53 suggest that multiple tumor development may be a "multifocal polyclonal process" rather than a monoclonal process "initiated by lateral movement" of premalignant cells, and state that "At present, there is no information as to which other tumor suppressor genes" might be among those that (along with p53) undergo genetic changes contributing to head and neck cancer progression (see page 4195, last paragraph). Thus, the teachings of the prior art suggest the manner in which cells containing the mutant nucleic acids of the claims might arise in lymph nodes and/or tumor margin tissues is not clear. Given the lack of evidence in both the specification and in the art with regard to how (or even whether) cells comprising the nucleic acids of the claims might spread to lymph nodes and/or tumor margin tissues, it cannot be predicted whether specimens taken from these locations that were found to contain detectable levels of such "mutant" nucleic acids would in fact fail to exhibit any "microscopic characteristics indicative of neoplastic

pathology." As noted above, many types of microscopy were available for use by those of skill in the art at the time the invention was made, and additional techniques such as staining and labeling may be employed with microscopy to increase its sensitivity. While it is certainly possible that such specimens might be identified, this question could only be resolved by further experimentation. Given the high level of skill of one skilled in the relevant art, it is clearly within the ability of such an artisan to conduct such further experimentation – however, the outcome cannot be predicted, and it is in fact possible that no quantity of experimentation would be sufficient to enable the claims. As it is unknown as to whether any quantity of experimentation would actually be sufficient to enable the practice of the claimed invention, it would clearly require an undue quantity of experimentation to use the invention of the instant claims.

***Claim Rejections - 35 USC § 102***

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

9. Claims 28-30 are rejected under 35 U.S.C. 102(a) as being anticipated by Nees et al (Cancer Research 53(18):4189-4196 [9/1993]).

Nees et al disclose methods for detecting p53 mutations in tumor, tumor-adjacent, and tumor-distant specimens from head and neck cancer patients (see entire reference). Nees et al's methods comprise steps of extracting nucleic acid from specimens and detecting p53 mutations present therein (see p. 4190). Nees et al

disclose that tumor-adjacent and tumor distant specimens did not exhibit neoplastic morphology (see, e.g., p. 4189-4190, 4194). The "tumor adjacent" specimens employed by Nees et al were obtained immediately after tumor removal (p. 4189), and constitute tumor margin specimens as well as tissues "from a surgical margin adjacent" to excised tumor. Nees et al disclose that mutated p53 nucleic acids were detected in such tumor adjacent samples (see, e.g., Table 3, p. 4191, 4193). With respect to claim 29, it is noted that the amplification and ISH methods of Nees et al at p. 4190 meet the limitations of the claim.

***Claim Rejections - 35 USC § 103***

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claim 31 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nees et al (Cancer Research 53(18):4189-4196 [9/1993]).

Nees et al disclose methods for detecting p53 mutations in tumor, tumor-adjacent, and tumor-distant specimens from head and neck cancer patients (see entire reference). Nees et al's methods comprise steps of extracting nucleic acid from specimens and detecting p53 mutations present therein (see p. 4190). Nees et al disclose that tumor-adjacent and tumor distant specimens did not exhibit neoplastic morphology (see, e.g., p. 4189). Nees et al do not disclose extraction and detection of p53 nucleic acids in lymph node tissues. However, Nees et al do note that multifocal

overexpression of p53 was observed in several patients "with $N_0$ tumors (no diagnosed regional lymph node metastases" (see p. 4191 and Table 2). In view of Nees et al's own teachings, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the invention of Nees et al so as to have extracted nucleic acids from the lymph node samples of these $N_0$ patients and to have detected and analyzed the p53 nucleic acids therein for changes indicative of cancer metastases. An ordinary artisan would have been motivated to have made such a modification in order to have determined whether p53 mutations such as those detected by Nees et al in tumor-adjacent and tumor distant specimens are also present in regional lymph nodes, for the advantage of further characterizing the manner in which cancer metastasis occurs (as discussed by Nees et al at page 4195).

12. Claims 12 and 18-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nees et al in view of Hamilton (Cancer 69(6 Suppl):1589-1591 [3/1992]).

It is noted that the instant claims do not include a limitation that the specimen "does not exhibit microscopic characteristics indicative of neoplastic pathology."

Nees et al disclose methods for detecting p53 mutations in tumor, tumor-adjacent, and tumor-distant specimens from head and neck cancer patients (see entire reference). Nees et al's methods comprise steps of extracting nucleic acid from specimens and detecting p53 mutations present therein (see p. 4190). Nees et al disclose that tumor-adjacent and tumor distant specimens did not exhibit neoplastic morphology (see, e.g., p. 4189-4190, 4194). The "tumor adjacent" specimens employed by Nees et al were obtained immediately after tumor removal (p. 4189), and

constitute tumor margin specimens as well as tissues "from a surgical margin adjacent" to excised tumor. Nees et al disclose that mutated p53 nucleic acids were detected in such tumor adjacent samples (see, e.g., Table 3, p. 4191, 4193). With respect to claim 12, it is noted that the amplification and ISH methods of Nees et al at p. 4190 meet the limitations of the claim. Nees et al do not teach a "neoplastic nucleic acid" selected from "APC, DCC, NF1, NF2, RET, VHL, and WT-1," as required by the claims. However, Nees et al note that their findings suggest that multiple tumor development may be a "multifocal polyclonal process" rather than a monoclonal process "initiated by lateral movement" of premalignant cells, and state that "At present, there is no information as to which other tumor suppressor genes" might be among those that (along with p53) undergo genetic changes contributing to head and neck cancer progression (see page 4195, last paragraph). Hamilton discloses that APC and DCC are 2 tumor suppressor genes that (like p53) are frequently found to be altered in colorectal carcinomas (see entire reference). In view of the teachings of Hamilton, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods of Nees et al so as to have assayed for the presence of genetic alterations in p53, APC, and DCC in surgical margin specimens taken from colorectal cancer patients. First, an ordinary artisan would have been motivated to have made such a modification in order to have determined whether various colorectal cancers develop and progress in a monoclonal and/or polyclonal manner, for the advantage of further elucidating the process of cancer progression, as suggested by Nees et al. Further, it is noted that Nees et al conclude that "It is to be

hoped that recognizing mutations in tumor-surrounding biopsy specimens and thereby identifying tumor patients at high risk of developing additional tumors will eventually improve the prognosis for these patients." Thus, an ordinary artisan would have been additionally motivated to have made the above described modification for the advantage of identifying individuals at increased risk of developing further tumors, thereby allowing for earlier treatment and improved prognosis for such patients, as suggested by Nees et al. It is further noted that regardless of the types of APC and/or DCC mutations detected in tumor margin specimens (i.e., regardless of whether mutations detected are indicative of lateral metastasis and/or a multifocal disease process), one of ordinary skill would recognize that the presence of cancer-related genetic abnormalities in surrounding tissues indicates the possibility of disease progression warranting further evaluation and treatment.

13. Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nees et al in view of Hamilton (Cancer 69(6 Suppl):1589-1591 [3/1992]), as applied to claims 12 and 18-19, above, in light of the teachings of Sobol et al (U.S. Patent No. 5,543,296 [8/6/1996; effective filing date 6/26/1991]).

The teachings of Nees et al and Hamilton et al are set forth in paragraph 13, above.

Nees et al disclose methods for detecting p53 mutations in tumor, tumor-adjacent, and tumor-distant specimens from head and neck cancer patients (see entire reference). Nees et al's methods comprise steps of extracting nucleic acid from specimens and detecting p53 mutations present therein (see p. 4190). Nees et al

disclose that tumor-adjacent and tumor distant specimens did not exhibit neoplastic morphology (see, e.g., p. 4189). The "tumor adjacent" specimens employed by Nees et al were obtained immediately after tumor removal (p. 4189), and constitute tumor margin specimens as well as tissues "from a surgical margin adjacent" to excised tumor. Nees et al disclose that mutated p53 nucleic acids were detected in such tumor adjacent samples (see, e.g., Table 3, p. 4191, 4193). It is noted that Nees et al do not disclose the sensitivity of PCR in detecting "neoplastic" nucleic acids. However, Sobol et al disclose that PCR is sufficiently sensitive to detect a target nucleic acid present in only 1 of 10,000 cells (col 2, lines 46-52). Accordingly, given the disclosure of Sobol et al, it is noted that it is an inherent property of the method of Nees et al that it meets the requirement of claim 13, in that the method would detect "no more than an average of about one out of every ten thousand cells of said tissue" having a "neoplastic" nucleic acid.

***Conclusion***

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is 571/272-0744. The examiner can normally be reached on Monday and Thursday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on 571/272-0745. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Diana B. Johannsen
Primary Examiner
Art Unit 1634